II. REMARKS

Formal Matters

Claims 34-38 and 40-86 are pending after entry of the amendments set forth herein.

Claims 34-41 were examined and were rejected. Claim 39 was objected to.

Claims 34-38, 40, and 41 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claims 34-38, 40, and 41 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 8, lines 15-17; page 13, lines 2-8; page 14, line 25 to page 15, line 10; page 39, lines 12-14. Accordingly, no new matter is added by these amendments.

Claim 39 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 42-86 are added. Support for new claims 42-86 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: claim 42: page 13, line 7; claims 43-46: page 15, lines 1-5; claims 47-58: page 8, lines 20-24; page 14, lines 5-10; Examples 10, 11, and 14; claims 59-86: claim 26 as originally filed; page 8, lines 16-19; and page 46, lines 14-23; claim 27 as originally filed; page 8, lines 16-19; and page 44, lines 13-27; and page 46, lines 14-15. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Information Disclosure Statement

The Office Action stated that the Information Disclosure Statement (IDS) filed on February 27, 2001 in this application fails to comply with 37 C.F.R.§1.98(a)(2). The Office Action stated that copies of cancelled references in the IDS were not provided in the instant case or in the parent application.

The IDS that the Office Action refers to was filed on July 18, 2003 along with the instant application. As provided for under 37 C.F.R. §1.98(d), copies of the references cited in the IDS filed on July 18, 2003 were not provided to the U.S. Patent Office, as all of the references were disclosed in parent application serial number 09/795,914. Application serial number 09/795,914 is in turn a

continuation of application serial number 08/916,935, which issued as U.S. Patent No. 6,193,963. Copies of the references cited in the July 18, 2003 IDS were also not provided to the Office, as they were provided in application serial number 08/916,935. Evidence that the references were provided to the Office in application serial number 08/916,935 is provided by the fact that the references are all cited on the face of U.S. Patent No. 6,193,963. Accordingly, the Office has access to these references in its files, and Applicants need not provide copies of same.

Claim objections

Claim 39 was objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim.

In the interest of expediting prosecution, claim 39 is canceled without prejudice to renewal, thereby rendering this objection moot.

Rejection under 35 U.S.C.§112, first paragraph

Claims 34, 36, 37, and 39 were rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the written description requirement.

The Office Action stated that the specification teaches only a partial structure of a single representative species of a plasma hyaluronidase polypeptide; and that the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of hyaluronidase polypeptide. Applicants respectfully traverse the rejection.

Comments regarding the written description requirement

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, paragraph 1 "Written Description" Requirement (Federal Register 66, No. 4, January 5, 2001; hereinafter the "Written Description Guidelines") provides instructions for examining patent applications for compliance with the written description requirement of 35 U.S.C.§112, first paragraph.

The Written Description Guidelines state:

(1) There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed;

(2) The Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims;

(3) Consequently, rejection of an original claim for lack of written description should be rare;

(4) An Examiner should review the entire application to understand how Applicant provides support for the claimed invention; and

(5) Such a review is conducted *from a standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art* (emphasis added).[1]

As stated in the Written Description Guidelines, "In most technologies which are mature, and *wherein the knowledge and level of skill in the art is high*, a written description question **should not be raised** for original claims even if the specification discloses only a method of making the invention and the function of the invention."

The Written Description Guidelines state that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species; and that a "representative number of species" means that the species which are adequately described are representative of the entire genus. The Written Description Guidelines state that **there may be situations in which one species adequately supports a genus**; and that **what constitutes a "representative number" is an inverse function of the skill and knowledge in the art.**[2]

The instant claims meet the written description requirement of 35 U.S.C.§112, first paragraph.

The instant specification provides ample description of human plasma hyaluronidase (hpHAse) polypeptides; and describes a number of identifying features of the enzyme. Specification, page 13, line 2 to page 14, line 4. These identifying features include, e.g., 1) β-1,4-endoglycosidase activity in the cleavage of hyaluronan; 2) a pH optimum of HAse activity of about 3.7; 3) a MW as determined by non-reducing SDS-PAGE of about 57 kDa; 4) a specific activity of at least 2 x 10^5 turbidity reducing units per mg protein; 5) an isoelectric point of pH 6.5; 6) partitioning into the Triton X-114 detergent-rich phase upon temperature-induced detergent phase extraction; 7) a fatty acid posttranslational modification; and 8) and at least two N-linked glycosylation sites.

[1] Written Description Guidelines, at page 1105.

The specification states that the term hpHAse encompasses polypeptides having amino acid sequences that are modified relative to a naturally-occurring amino acid sequence of hpHase due to amino acid substitution, deletion, and/or addition. Specification, page 13, line 25 to page 14, line 1. The specification further states that hpHAse polypeptides preferably are biologically active. Specification, page 14, lines 2-3. The specification provides ample detail as to how to determine whether an hpHAse polypeptide is biologically active. See, e.g., specification, Example 2. The skill level of those in the art of generating polypeptides with variant amino acid sequences and testing their biological activity was very high as of the October 17, 1996 priority date.

The specification provides **two** amino acid sequences of hpHAse polypeptides. Specification, page 13, lines 15-25; page 33, lines 9-11; page 33, lines 23-29; and SEQ ID NOs:1 and 3. Applicants submit that, given 1) the disclosure of two hpHAse polypeptide amino acid sequences; 2) the high skill level of those in the art with respect to identifying variants of polypeptides; and 3) the disclosure in the specification of several identifying features of hpHAse polypeptides, those skilled in the art would reasonably conclude that the Applicants had possession of the claimed invention.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 34, 36, 37, and 39 under 35 U.S.C.§112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(b)

Claims 34-41 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Afify et al. ((1993) *Arch. Biochem. Biophys.* 305:434-441; "Afify").

The Office Action stated: 1) Afify teaches the purification of hyaluronidase from fresh human serum as starting material to apparent homogeneity in a two-step procedure; and 2) this enzyme has an apparent molecular weight of 59 kD when assayed by SDS-PAGE. The Office Action stated that "[g]iven the similarity of the substrate (hyaluronic acid) used to assay hyaluronidase activity," the examiner "has drawn a correlation between the functional characterization of the native hyaluronidase polypeptide, and structural elements such as glycosylation and fatty acid modification as inherent

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[2] Written Description Guidelines, page 1106.

properties of the native hyaluronidase polypeptide." Office Action, page 4. Applicants respectfully traverse the rejection.

The instant invention relates to highly purified hpHAse. The hpHAse is purified to a degree not previously disclosed. The material discussed in Afify is a crude preparation, and as such contains plasma protein contaminants. Indeed, Afify indicates that the hpHAse composition discussed therein exhibited a specific activity of only 53.3 units per mg protein. Afify, page 438, Table 1. Afify does not disclose a composition comprising a hpHAse that is purified to a degree disclosed in the instant application, where the hpHAse is substantially pure. Accordingly, Afify cannot anticipate the instant invention as claimed.

The Office Action stated that "the relative activity of the enzyme is presumed to be the same as the enzyme of Afify." Office Action, page 4. However, the specific activity is an expression of the level of purity and activity of the enzyme. The composition disclosed in Table 1 exhibited a specific activity of only 53.3 units per mg protein; an hpHAse composition discussed in Afify does not contain the same level of enzymatically active, substantially pure hpHAse as the compositions as claimed in the instant invention. Accordingly, Afify cannot anticipate claims 34-41.

Because the hpHAse preparation of Afify was a crude preparation and therefore contained many plasma protein contaminants, Afify could not have determined whether the hpHAse discussed therein possessed any glycosylations and/or fatty acid modifications.

Nevertheless, and solely in the interest of expediting prosecution, claim 34 is amended to recite a composition comprising a **substantially pure** hpHAse polypeptide. Afify does not disclose a composition comprising substantially pure hpHAse. Accordingly, Afify cannot anticipate the instant invention as claimed.

Applicants further note that, as discussed in the instant specification, previous attempts to isolate hpHAse from human serum have met with limited success, due in part to the inability to obtain purified hpHAse that is stable and has high specific activity. Specification, page 4, line 23 to page 5, line 1. Accordingly, a composition comprising substantially pure hpHAse polypeptide that is enzymatically active and that is glycosylated is also not obvious in view of the crude preparation discussed in Afify.

Applicants submit that the rejection of claims 34-41 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSF-088 CON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Feb. 28, 2005

By: _____
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